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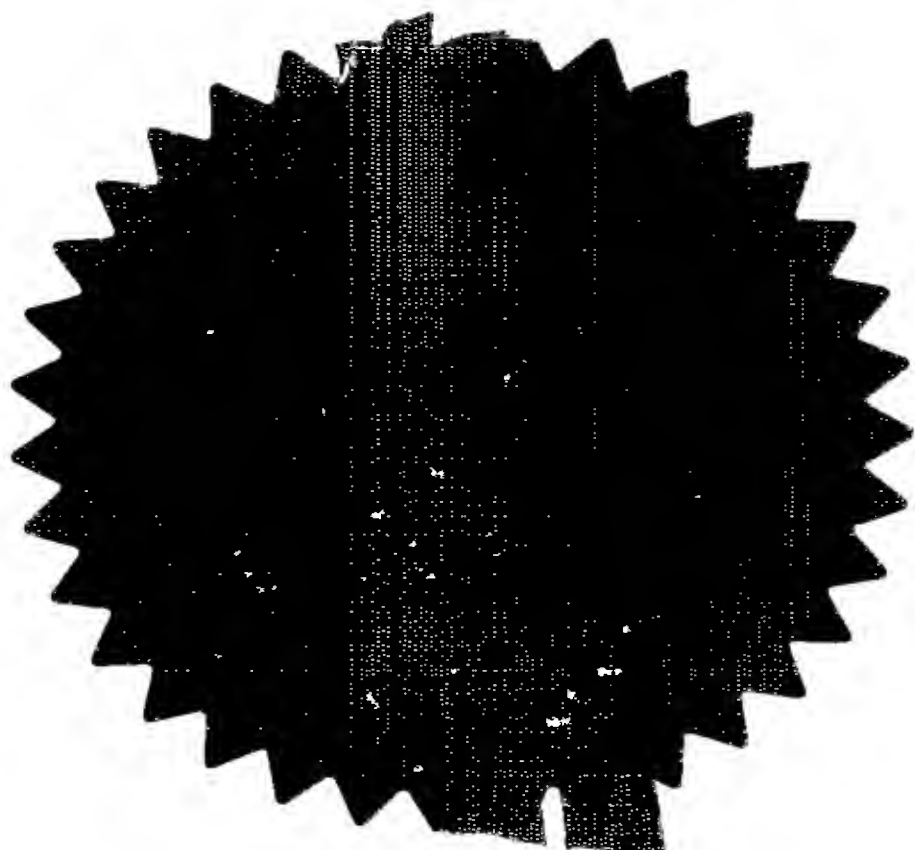
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Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its incorporation	UK	8157847001	
4. Title of the invention	Degradation Protectors		
5. Name of your agent (if you have one)	J.A. KEMP & CO.		
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J.A. Kemp & Co.

Date 5 March 2004

J.A. KEMP & CO.

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DEGRADATION PROTECTORS

The present invention relates to degradation protectors in UV screening compositions suitable for cosmetic and topical pharmaceutical use.

The effects associated with exposure of the skin to UVA and UVB light are well known and include, for example, sunburn, premature ageing and skin cancer.

Commercial sunscreens generally contain components which are able to reflect and/or absorb UV light. These components include, for example, inorganic oxides such as zinc oxide and titanium dioxide as well as organic sunscreen agents.

The general public are generally more concerned by the obvious effects of sunlight, namely sunburn which causes reddening of the skin than they are with other effects of sunlight which are less self evident. As a consequence of this commercial sunscreen compositions are rated by a Sun Protection Factor (SPF). This is a measure of the time taken for skin to redden under a layer of the composition as compared with untreated skin. Thus an SPF of 20 indicates that skin will take 20 times longer to redden under a layer of the composition applied at 2mg per cm² compared with untreated skin. This reddening effect is caused principally by UVB light. There is no recognised corresponding factor for the effects of UVA light even though the latter may be more damaging in the long term.

Most organic sunscreen agents absorb light over only a part of the UVA-UVB spectrum with the result that if one is to obtain a screening effect covering the whole UVA-UVB spectrum it is generally necessary to use a combination of different organic sunscreen agents. Some organic sunscreen agents and other components of sunscreen compositions are stable to UV light but others are photosensitive and/or may after being excited by UV light result in the formation of free radicals which may attack and cause degradation of another ingredient of the composition.

Titanium dioxide and zinc oxide are generally formulated as "micronised" or "ultrafine" (20-50 nm) particles (so-called microreflectors) because particles whose size is less than 10% of the wavelength of the incident light scatter light according to Rayleigh's Law, whereby the intensity of scattered light is inversely proportional to the fourth power of the wavelength. Consequently, they scatter UVB light (with a wavelength of from 280 or 290 to 315/ 320 nm) and UVA light (with a wavelength of

from 315/320 to 400 nm) more than the longer, visible wavelengths, preventing sunburn whilst remaining invisible on the skin.

However, titanium dioxide and zinc oxide also absorb UV light efficiently, leading via the initial formation of electron hole pairs to the formation of superoxide and hydroxyl radicals in contact with water, which may in turn initiate damage to other components of the composition. The crystalline forms of TiO_2 , anatase and rutile, are semiconductors with band gap energies of about 3.23 and 3.06 eV respectively, corresponding to light of about 385 nm and 400 nm (1 eV corresponds to 8066 cm^{-1}). Indeed there is evidence to suggest that TiO_2 can enhance the degradation of organic sunscreen agents, including UVA organic sunscreens, for example avobenzene (butyl methoxydibenzoyl methane, also known as BMDM). Attempts have been made to reduce the adverse effects of TiO_2 and ZnO by coating but coatings are not invariably effective.

The reason why most sunscreen agents do not have a substantially perpetual effect (i.e. an SPF factor which remains substantially constant) is principally because the organic sunscreen agents are degraded by light and/or are adversely affected by other components of the sunscreen composition once the latter are subjected to UV light.

In our British Application No. 0315082.8 we describe how the degradation of organic sunscreen agents, and other components which are susceptible to degradation, can be retarded if the compositions also have present zinc oxide or titanium dioxide which has been doped with another element and/or reduced zinc oxide. These can be regarded as degradation protectors because they help to protect sunscreen ingredients which are unstable to sunlight against sunlight-induced photo-degradation. By using these doped or reduced materials rather than ordinary titanium dioxide or zinc oxide it is, for example, possible either to provide a composition which gives better protection against UV light for the same quantity of organic sunscreen agent or a composition having the same screening effect against UV light but containing a smaller quantity of organic sunscreen agent. Indeed it is possible to provide all day protection sunscreens by incorporating the doped and/or reduced materials. Sometimes the degradation products (breakdown chemicals) are toxic.

Accordingly, the present invention also provides method of reducing the production of toxic compounds in a UV sunscreen composition which comprises incorporating therein a doped TiO_2/ZnO and/or reduced ZnO . In general the composition containing the doped $\text{TiO}_2 / \text{ZnO}$ has a rate of loss of UV absorption at least 5%
5 preferably at least 10%, more preferably at least 15%, especially at least 20% and most preferably at least 40%, less than that of a composition having the same formulation except that it does not contain the doped material. Thus if the rate of loss of UV absorption (during UV exposure) over at least a proportion of the UVA and/or UVB spectrum is X then the amount of the organic component(s) which are
10 photosensitive and/or which are degraded by another ingredient of the composition possesses a said rate of loss of Y where Y is greater than X by at least 5%, and the amount of doped TiO_2 and/or ZnO reduces the said rate of loss from Y to X.

It has now been appreciated, according to the present invention, that it is important that if the oxide is to be really effective there must be dopant on its surface
15 which can interact with the component of the composition to be protected. For example if, in a two phase composition, the oxide is present in the aqueous phase and the component to be protected is in the organic phase there is little interaction because of the phase boundary; the oxide is not accessible to the component. Thus the free radicals generated by degradation of the component cannot contact the
20 dopant without changing phase. It has further been realised that if the dopant is solely in the bulk it is not able to interact effectively (as a free radical scavenger) with the component of the composition to be protected. A consequence of this is that it is possible to use materials which are only surface doped i.e where there is dopant in or on the surface of the particle. In one embodiment such materials may be used in a
25 single phase formulation. Although the presence of bulk dopant is desirable where the composition is intended to protect the skin, because the dopant is able to trap free radicals generated by the action of UV light and dissipate the energy produced, this is not essential for a formulation which is not intended to have a skin protection effect. It should be added that the effect of bulk dopant occurs regardless of the phase in
30 which the particle is placed, in contrast to surface dopant.

Accordingly the present invention provides (although not dependant on the above theory) a UV sunscreen composition suitable for cosmetic or topical pharmaceutical use which comprises: (a) one or more organic components which are photosensitive and/or which are susceptible to degradation by another ingredient of the composition and/or by undoped TiO_2 and/or by undoped ZnO ; and (b) TiO_2 and/or ZnO which has been surface doped with one or more other elements, typically one i.e. a second element. Where the particle has been bulk doped there will, in general, be dopant throughout the particle. On the other hand where the particle has been "surface doped" (i.e. the dopant is only in or on the surface) there will be a concentration gradient e.g. such that the ratio of dopant atoms to titanium or zinc atoms at the surface or outmost "skin" of the particle is greater than the ratio in the core or centre where it may be zero.

By "UV sunscreen composition suitable for cosmetic or topical pharmaceutical use" is meant any cosmetic or topical pharmaceutical composition having UV sunscreen activity i.e. it includes compositions whose principal function may not be suncreening. It will be appreciated that the doped TiO_2/ZnO or reduced ZnO may be the only ingredient of the composition having UV sunscreen activity i.e. the composition need not necessarily contain an organic UV sunscreen agent. It is to be understood that the composition can also contain TiO_2 and/or ZnO which has not been doped or reduced.

The organic component which is photosensitive or degraded by another ingredient of the composition is generally a UV sunscreen agent. Although all organic sunscreen agents which suffer a loss in UV absorption can be used, the present invention is particularly useful for agents which absorb in the UVA region as well as in the UVB region. However, other organic components will generally be susceptible to free radical attack and in turn this generally may cause degradation of the UV sunscreen agent.

As indicated above the UV absorption of an organic sunscreen agent generally decreases with time. In contrast, the UV absorption of TiO_2 or ZnO does not decrease with time. Since TiO_2 and ZnO absorb in both the UVA and UVB

region whereas an organic sunscreen agent is generally more wavelength specific, it can be seen that the UVA/UVB absorption ratio may change over time. For example, as is preferred, where the organic sunscreen agent absorbs in the UVA region, then the ratio will decrease over time. When doped TiO_2/ZnO is used, rather than the same quantity of undoped TiO_2/ZnO , the rate of change is reduced. This is because the doped material will enhance the performance of the organic sunscreen agent over time relative to the situation where undoped TiO_2/ZnO is present. Thus with a UVA sunscreen the loss of UVA absorption over time is reduced (i.e. the UVA response is more stable when the doped material is present) so that the ratio of change of the rates is reduced. Thus if the initial ratio of absorption is X/Y , it becomes $(X-x)/Y$ where x is smaller when a doped material is used, with the result that the rate of change is less. With a UVB sunscreen, the rate of change is also reduced as a consequence of a more stable UVB response.

The rate of loss of absorption can be determined by illuminating a sample of the composition with and without the doped TiO_2 and/or ZnO of defined thickness with UV light, as discussed in British Application No. 0315082.8.

It will be appreciated that although it will normally be the case that the bulk dopant will be the same element as the surface dopant (for simplicity of preparation), this need not necessarily be the case. (Of course, with reduced zinc oxide there is no bulk dopant.) By this means it is possible, for example, to modify the colour of the particles. Suitable dopants for the oxide particles include manganese, which is especially preferred, e.g. Mn^{2+} and Mn^{4+} but especially Mn^{3+} , vanadium, for example V^{3+} or V^{5+} , chromium and iron, but other metals which can be used include nickel, copper, tin, aluminium, lead, silver, zirconium, zinc, cobalt, gallium, niobium, for example Nb^{5+} , antimony, for example Sb^{3+} , tantalum, for example Ta^{5+} , strontium, calcium, magnesium, barium, molybdenum, for example Mo^{3+} , Mo^{5+} or Mo^{6+} as well as silicon. Manganese is preferably present as Mn^{3+} , cobalt as Co^{2+} , tin as Sn^{4+} as well as Mn^{2+} . These metals can be incorporated singly or in combination of 2 or 3 or more. It will be appreciated that for effective bulk doping the size of the ion must be such as can readily be inserted into the crystal lattice of the particle. For this purpose Mn^{3+} , vanadium, chromium and iron are generally the most effective; the ionic size

of Mn^{2+} is much larger than that of Ti^{4+} and so there is little probability of ionic diffusion of Mn^{2+} into the TiO_2 crystal lattice. On the other hand there is no such size limitation for the elements used in surface doping; preferred surface dopants include manganese, eg. as Mn^{2+} , cerium, selenium, chromium and iron as well as vanadium, typically as V^{4+} .

The optimum total amount of the second component on, and, if present, in, the particle may be determined by routine experimentation but it is preferably low enough so that the particles are minimally coloured. Amounts as low as 0.1 mole % or less, for example 0.05 mole %, or as high as 1 mole % or above, for example 5 mole % or 10 mole %, can generally be used. Typical concentrations are from 0.5 to 2 mole % by weight. The mole ratio of dopant to host metal on the surface is typically from 2-25:98-75, usually 5-20:95-80 and especially 8-15:92-85. The amount of dopant at the surface can be determined by, for example, X-ray Photoelectron Spectroscopy (XPS).

The surface-doped particles can be obtained by any one of the standard processes for preparing such doped oxides and salts. These include techniques such as those described below. It will be appreciated that the dopant need not necessarily be present as an oxide, but may be present as a salt such as a chloride or as a salt with an oxygen-containing anion such as perchlorate or nitrate. However bulk doping techniques will generally result in some surface doping as well, and these techniques can be used in the present invention. Such techniques include a baking technique by combining particles of a host lattice (TiO_2/ZnO) with a second component in the form of a salt such as a chloride or an oxygen-containing anion such as a perchlorate or a nitrate, in solution or suspension, typically in solution in water, and then baking it, typically at a temperature of at least 300°C . Other routes which may be used to prepare the doped materials include a precipitation process of the type described in J. Mat. Sci. (1997) 36, 6001-6008 where solutions of the dopant salt and of an alkoxide of the host metal (Ti/Zn) are mixed, and the mixed solution is then heated to convert the alkoxide to the oxide. Heating is continued until a precipitate of the doped material is obtained. Further details of preparation can be found in WO 00/60994 and WO 01/40114.

It will be appreciated that such baking techniques and the like will result in dopant in the surface forming part of the crystal lattice while in other techniques the dopant will merely be adsorbed, or remain as a separate layer, on the particle surface. It may well be the case that if the dopant is to quench internally generated free radicals effectively then it needs to be in the crystal lattice.

The rutile form of titania is known to be less photoactive than the anatase form and is therefore preferred.

Doped TiO_2 or doped ZnO may be obtained by flame pyrolysis or by plasma routes where mixed metal containing precursors at the appropriate dopant level are exposed to a flame or plasma to obtain the desired product.

The zinc oxide subjected to surface doping can be reduced zinc oxide (where a skin protecting effect is desired). Reduced zinc oxide particles (i.e. particles which possess an excess of zinc ions relative to the oxygen ions) may be readily obtained by heating zinc oxide particles in a reducing atmosphere to obtain reduced zinc oxide particles which absorb UV light, especially UV light having a wavelength below 390 nm, and re-emit in the green, preferably at about 500 nm. Typically the concentration of hydrogen is from 1 to 20%, especially 5 to 15%, by volume, with the balance inert gas, especially nitrogen. A preferred reducing atmosphere is about 10% hydrogen and about 90% nitrogen by volume. The zinc oxide is heated in this atmosphere at, say, 500° to 1000° C, generally 750 to 850° C, for example about 800° C, for 5 to 60 minutes, generally 10 to 30 minutes. Typically it is heated to about 800° C for about 20 minutes. It will be understood that the reduced zinc oxide particles will contain reduced zinc oxide consistent with minimising migration to the surface of the particles of electrons and/or positively charged holes such that when said particles are exposed to UV light in an aqueous environment the production of hydroxyl radicals is substantially reduced as discussed above.

It is believed that the reduced zinc oxide particles possess an excess of Zn^{2+} ions within the absorbing core. These are localised states and as such may exist within the band gap. A further discussion of this can be found in WO 99/60994.

The average primary particle size of the particles is generally from about 1 to 200 nm, for example about 1 to 150 nm, preferably from about 1 to 100 nm, more

preferably from about 1 to 50 nm and most preferably from about 20 to 50 nm. The particle size is preferably chosen to prevent the final product from appearing coloured. Thus nanoparticles are frequently used. Since the scavenging effect is believed to be essentially catalytic it is desirable that the particles are as small as possible to maximise their surface area and hence the area of doped material on the surface. This small size has the advantage that less dopant is needed which has the consequential advantage that any colouring effect caused by the dopant is reduced. However, in one embodiment slightly larger particles for example from 100 to 500 nm, typically 100 to 400 or 450 nm especially from 150 to 300 nm and particularly 200 to 250 nm, can be employed. These provide good coverage of, for example, skin imperfections without unacceptable skin whitening.

Where particles are substantially spherical then particle size will be taken to represent the diameter. However, the invention also encompasses particles which are non-spherical and in such cases the particle size refers to the largest dimension.

The oxide particles used in the present invention may have an inorganic or organic coating. For example, the particles may be coated with oxides of elements such as aluminium, zirconium or silicon, especially silica or, for example, aluminium silicate. The particles of metal oxide may also be coated with one or more organic materials such as polyols, amines, alkanolamines, polymeric organic silicon compounds, for example, $\text{RSi}[\{\text{OSi}(\text{Me})_2\}_x\text{OR}^1]_3$ where R is $\text{C}_1\text{-C}_{10}$ alkyl, R^1 is methyl or ethyl and x is an integer of from 4 to 12, hydrophilic polymers such as polyacrylamide, polyacrylic acid, carboxymethyl cellulose and xanthan gum or surfactants such as, for example, TOPO. If desired the surface doping can be carried out by a coating technique either separately or in combination with the inorganic or organic coating agent. Thus for example the undoped oxide can be coated with, say, manganese oxide along with an organic or inorganic coating agent such as silica. It is generally unnecessary to coat the oxide particles to render them hydrophilic so that for the aqueous phase the particles can be uncoated. However if the particles are to be in the organic or oily phase their surface needs to be rendered hydrophobic or oil-dispersible. This can be achieved by the application directly of, for example, a suitable hydrophobic polymer or indirectly by the application of a coating, for

example of an oxide such as silica (which imparts a hydrophilic property) to which a hydrophobic molecule such as a metal soap or long chain (e.g. $C_{12} - C_{22}$) carboxylic acid or a metal salt thereof such as stearic acid, a stearate, specifically aluminium stearate, aluminium laurate and zinc stearate.

- 5 It should be understood that the term "coating" is not to be construed as being limited to a complete covering. Indeed it is generally beneficial for the coating not to be complete since the coating can act as a barrier to the interaction of the free radicals with the dopant on or in the surface of the particle. Thus it is preferred that the coating should be discontinuous where maximum scavenging effect is desired.
- 10 However it will be appreciated that dopant on the surface can still act to quench free radicals generated within the particle in which case the coating can be continuous.. Since coatings of silanes and silicones which can be polymeric or short chain or monomeric silanes are generally continuous these are generally less preferred. Thus coating with an inorganic oxide is generally preferred since these generally do not
- 15 result in a complete coating on the surface of the particles.

Typical coating procedures include the deposition of silica by mixing alkali such as ammonium hydroxide with an orthosilicate, such as tetraethylorthosilicate, in the presence of the particle. Alternatively the particle can first be coated with a silane such as (3-mercaptopropyl) trimethoxy silane (MPS) and then silicate e.g.

20 sodium silicate is added. The silane attaches to the particle surface and acts as a substrate for the silicate which then polymerises to form silica. Preferably the material is extracted by freeze-drying because such a sublimation technique reduces hydrogen bond formation thereby keeping the particles small. A typical procedure is as follows:

- 25 a) 4.52g of titania are added to 200ml deionised water. An ultrasonic horn is used to disperse the material.
- b) 1.89ml (3-mercaptopropyl)trimethoxy silane [MPS] is added to 50ml water under vigorous stirring
- c) 20ml of the MPS solution is added to the titania solution under vigorous

stirring. This solution is stirred for two hours to allow the MPS to attach to the surface.

d) 40ml 25% sodium silicate solution is added and the solution is stirred for one hour. The silica slowly deposits upon the MPS layer.

5 e) The titania is removed by centrifugation and washed three times in deionised water.

f) The material is freeze dried. A few nm layer of silica is thereby coated to the titania surface.

Similar techniques can be used for other inorganic oxides.

10 The compositions of the present invention can be single phase, either aqueous or oily or multiphase. Typical two-phase compositions comprise oil-in-water or water-in-oil formulations. For single phase compositions the oxide particles must of course be dispersible in that phase. Thus the particles are desirably hydrophilic if the composition is aqueous or hydrophobic if the composition is oil-based. However it
15 may be possible to disperse untreated TiO_2 in the oily phase by appropriate mixing techniques. For two or multi-phase composition the particles must be present in the phase containing the ingredient (or one of those ingredients) to be protected. It can, though, be desirable for the particles to be present in both aqueous and oily phases even if no ingredients which are to be protected are present in one of those phases.
20 This can cover the situation where application of the composition by the user results in some phase transfer of the ingredient(s) to be protected. Also, when an emulsion is spread on the skin it has a tendency to break down into oily and non-oily areas. When the water evaporates the oil-dispersible particles will tend to be in the oily areas thus leaving areas unprotected. This can be avoided by having both hydrophilic
25 and hydrophobic particles in the emulsion so that some are retained in hydrophilic areas and others in hydrophobic areas. Desirably, the weight ratio of the water-dispersible particles to the oil-dispersible particles is from 1:4 to 4:1, preferably from 1:2 to 2:1 and ideally about equal weight proportions. Many organic sunscreens are

hydrophobic so that the particles should be hydrophobic but some organic sunscreens by virtue of, in particular, acid groups are water soluble in which case the particles need to be hydrophilic in order to protect them.

The compositions of the present invention are generally for cosmetics use and
5 may be, for example, skin tanning compositions in the form of, for example, creams, lipsticks, skin anti-ageing compositions in the form of, for example, creams, including anti-wrinkle formulations, exfoliating preparations including scrubs, creams and lotions, skin lightening compositions in the form of, for example, face
10 creams, preparations for the hands including creams and lotions, moisturising preparations, compositions for protecting the hair such as conditioners, shampoos and hair lacquers as well as hair masks and gels, skin cleansing compositions including wipes, lotions and gels, eye shadow and blushers, skin toners and serums as well as washing products such as shower gels, bath products including bubble baths, bath oils, but, preferably, sunscreens. In this connection we should point out that the
15 expression "cosmetic UV sunscreen composition", as used herein, includes any composition applied to the skin which may leave a residue on the skin such as some washing products. Compositions of the present invention may be employed as any conventional formulation providing protection from UV light. The composition may also be pharmaceutical compositions suitable for topical application. Such
20 compositions are useful, in particular, for patients suffering from disorders of the skin which are adversely affected by UV light such as those giving rise to polymorphous light eruptions.

Organic sunscreen agents which can be used in the compositions of the present invention include any conventional sunscreen agent which gives protection
25 against UV light while if there is no other photosensitive component the sunscreen agent is photosensitive and/or is degraded by another ingredient of the composition. Suitable sunscreen agents are listed in the IARC Handbook of Cancer Prevention, vol. 5, Sunscreens, published by the International Agency for Research on Cancer, Lyon, 2001 and include:

- 30 (a) Para-aminobenzoic acids (PABA), (UVB absorbers) esters and

derivatives thereof, for example amyldimethyl-;
ethyldihydroxypropyl-; ethylhexyl dimethyl-; ethyl-; glyceryl-; and 4-
bis-(polyethoxy)- PABA.

- 5 (b) Cinnamates (UVB) especially esters including methyl cinnamate
esters and methoxycinnamate esters such as octylmethoxy cinnamate,
ethyl methoxycinnamate, especially 2-ethylhexyl para-
methoxycinnamate, isoamyl p-methoxy cinnamate, or a mixture
thereof with diisopropyl cinnamate, 2-ethoxyethyl -4-
methoxycinnamate, DEA-methoxycinnamate (diethanolamine salt of
10 para-methoxy hydroxycinnamate) or α,β -di-(para-methoxycinnamoyl)-
 α' -(2-ethylhexanoyl)-glycerin, as well as diisopropyl methylcinnamate;
- (c) benzophenones (UVA) such as 2,4-dihydroxy-; 2-hydroxy-4-methoxy;
2,2'-dihydroxy-4,4'-dimethoxy-; 2,2'-dihydroxy-4-methoxy-; 2,2',4,4'-
tetrahydroxy-; and 2-hydroxy-4-methoxy-4'-methyl-benzophenones,
15 benzenesulphonic acid and its sodium salt; sodium 2,2'-dihydroxy-
4,4'-dimethoxy-5-sulphobenzophenone and oxybenzone
- (d) dibenzoylmethanes (UVA) such as butyl methoxydibenzoyl methane
(BMDM, referred to herein as avobenzene), especially 4-tert-butyl-
4'methoxydibenzoyl methane;
- 20 (e) 2-phenylbenzimidazole-5 sulfonic acid UVB and
phenyldibenzimidazole sulfonic acid and their salts;
- (f) alkyl- β,β -diphenylacrylates (UVB) for example alkyl α -cyano- β,β -
diphenylacrylates such as octocrylene;
- (g) triazines (UVB) such as 2,4,6-trianilino-(p-carbo-2-ethyl-hexyl-1-
25 oxy)-1,3,5 triazine as well as octyl triazone e.g. ethylhexyltriazone and
diethylhexyl butamido triazone.
- (h) camphor derivatives (generally UVB) such as 4-methylbenzylidene
and 3-benzylidene- camphor and terephthalylidene dicamphor
sulphonic acid (UVA), benzylidene camphor sulphonic acid, camphor
30 benzalkonium methosulphate and polyacrylamidomethyl benzylidene

camphor;

- (i) organic pigment sunscreens such as methylene bis-benzotriazole tetramethyl butylphenol;
- (j) silicone based sunscreens such as dimethicodiethyl benzal malonate.
- (k) salicylates (UVB) such as dipropylene glycol-, ethylene glycol-, ethylhexyl-, isopropylbenzyl-, methyl-, phenyl-, 3,3,5-trimethyl- and TEA-salicylate (compound of 2-hydroxybenzoic acid and 2,2'2"-nitrilotris (ethanol));
- (l) anthranilates (UVA) such as menthyl anthranilate as well as bisymidazylate (UVA), dialkyl trioleate (UVB), 5-methyl-2 phenylbenzoxazole (UVB) and urocanic acid (UVB).

Some compounds are effective for both UVA and UVB. These include methylene bisbenzotriazolyl tetramethylbutyl-phenol and drometrizole trisiloxane (Mexoryl XL).

The organic sunscreen agent(s) are typically present in the compositions at a concentration from 0.1 to 20%, preferably 1 to 10%, and especially 2 to 5%, by weight based on the weight of the composition.

In the compositions, the metal oxides are preferably present, in the phase or phases where they are present, at a concentration of about 0.5 to 20 % by weight, preferably about 1 to 10 % by weight and more preferably about 3 to 8 % by weight, in particular about 4 to 7%, such as 4 to 6% for example about 5%, by weight.

The compositions may be in the form of, for example, lotions, typically with a viscosity of 4000 to 10,000 mPas, e.g. thickened lotions, gels, vesicular dispersions, creams, typically a fluid cream with a viscosity of 10,000 to 20,000 mPas or a cream of viscosity 20,000 to 100,000 mPas, milks, powders, solid sticks, and may be optionally packaged as aerosols and provided in the form of foams or sprays.

The compositions may contain any of the ingredients used in such formulations including fatty substances, organic solvents, silicones, thickeners, liquid and solid emollients, demulcents, other UVA, UVB or broad-band sunscreen agents, antifoaming agents, antioxidants such as butyl hydroxy toluene, buffers such as lactic

acid with a base such as triethanolamine or sodium hydroxide, plant extracts such as Aloe vera, cornflower, witch hazel, elderflower and cucumber, activity enhancers, moisturizing agents, and humectants such as glycerol, sorbitol, 2-pyrrolidone-5-carboxylate, dibutylphthalate, gelatin and polyethylene glycol, perfumes, preservatives, such as para-hydroxy benzoate esters, surface-active agents, fillers and thickeners, sequesterants, anionic, cationic, nonionic or amphoteric polymers or mixtures thereof, propellants, alkalizing or acidifying agents, colorants and powders, including metal oxide pigments with a particle size of from 100 nm to 20000 nm such as iron oxides along with conventional (undoped) TiO_2 and ZnO .

It is known that other ingredients of cosmetic compositions, for example some surface-active agents may have the effect of degrading certain sunscreen agents in the presence of UV light. Also TiO_2 and ZnO are known to degrade certain organic sunscreens such as avobenzone as well as antioxidants such as vitamins e.g. vitamins A, B, C and E. It will be appreciated that it is particularly useful to use the doped TiO_2 and/or ZnO and/or reduced ZnO with such sunscreens. This is because TiO_2 and ZnO do generally have a positive UV absorptive effect. Thus by using the doped TiO_2 and/or ZnO and/or reduced ZnO it may be possible to use less antioxidant or make the formulation longer lasting.

The organic solvents typically comprise lower alcohols and polyols such as ethanol, isopropanol, propylene glycol, glycerin and sorbitol as well as methylene chloride, acetone, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol mono-ethyl, ether, dimethyl sulphoxide, dimethyl formamide and tetrahydrofuran.

The fatty substances may comprise an oil or wax or mixture thereof, fatty acids, fatty acid esters, fatty alcohols, vaseline, paraffin, lanolin, hydrogenated lanolin or acetylated lanolin, beeswax, ozokerite wax and paraffin wax.

The oils typically comprise animal, vegetable, mineral or synthetic oils and especially hydrogenated palm oil, hydrogenated castor oil, vaseline oil, paraffin oil, Purcellin oil, silicone oil such as polydimethyl siloxanes and isoparaffin.

The waxes typically comprise animal, fossil, vegetable, mineral or synthetic waxes. Such waxes include beeswax, Carnauba, Candelilla, sugar cane or Japan

waxes, ozokerites, Montan wax, microcrystalline waxes, paraffins or silicone waxes and resins.

The fatty acid esters are, for example, isopropyl myristate, isopropyl adipate, isopropyl palmitate, octyl palmitate, C₁₂-C₁₅ fatty alcohol benzoates ("FINSOLV TN" from FINETEX), oxypropylenated myristic alcohol containing 3 moles of propylene oxide ("WITCONOL APM" from WITCO), capric and caprylic acid triglycerides ("MIGLYOL 812" from HULS).

The compositions may also contain thickeners such as cross-linked or non cross-linked acrylic acid polymers, and particularly polyacrylic acids which are cross-linked using a polyfunctional agent, such as the products sold under the name "CARBOPOL" by the company GOODRICH, cellulose, derivatives such as methylcellulose, hydroxymethylcellulose, hydroxypropyl methylcellulose, sodium salts of carboxymethyl cellulose, or mixtures of cetylstearyl alcohol and oxyethylenated cetylstearyl alcohol containing 33 moles of ethylene oxide.

Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, eicosanyl alcohol behenyl alcohol, cetyl palmitate, silicone oils such as dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, cocoa butter, corn oil, cotton seed oil, olive oil, palm kernel oil, rapeseed oil, safflower seed oil, evening primrose oil, soybean oil, sunflower seed oil, avocado oil, sesame seed oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum jelly, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate.

Suitable propellants include propane, butane, isobutane, dimethyl ether, carbon dioxide, nitrous oxide.

Suitable powders include chalk, talc, fullers earth, kaolin, starch, gums, colloidal silica sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified

montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate.

When the compositions of the present invention are sunscreens they may be in the form of, for example, suspensions or dispersions in solvents or fatty substances
5 or as emulsions such as creams or milks, in the form of ointments, gels, solid sticks or aerosol foams. The emulsions, which can be oil-in-water or water-in-oil emulsions, may further contain an emulsifier including anionic, nonionic, cationic or amphoteric surface-active agents; for a water-in-oil emulsion the HLB is typically from 1 to 6 while a larger value i.e >6 is desirable for an oil-in-water emulsion.
10 Generally water amounts to up to 80%, typically 5 to 80%, by volume. Specific emulsifiers which can be used include sorbitan trioleate, sorbitan tristearate, glycerol monooleate, glycerol monostearate, glycerol monolaurate, sorbitan sesquioleate, sorbitan monooleate, sorbitan monostearate, polyoxyethylene (2) stearyl ether, polyoxyethylene sorbitol beeswax derivative, PEG 200 dilaurate, sorbitan
15 monopalmitate, polyoxyethylen (3.5) nonyl phenol, PEG 200 monostearate, sorbitan monostearate, sorbitan monolaurate, PEG 400 dioleate, polyoxyethylene (5) monostearate, polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (4) lauryl ether, polyoxyethylene (5) sorbitan monooleate, PEG 300 monooleate, polyoxyethylene (20) sorbitan tristearate, polyoxyethylene (20) sorbitan trioleate,
20 polyoxyethylene (8) monostearate, PEG 400 monooleate, PEG 400 monostearate, polyoxyethylene (10) monooleate, polyoxyethylene (10) stearyl ether, polyoxyethylene (10) cetyl ether, polyoxyethylene (9.3) octyl phenol, polyoxyethylene (4) sorbitan monolaurate, PEG 600 monooleate, PEG 1000 dilaurate, polyoxyethylene sorbitol lanolin derivative, polyoxyethylene (12) lauryl
25 ether, PEG 1500 dioleate, polyoxyethylene (14) laurate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, polyoxyethylene (20) stearyl ether, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) cetyl ether, polyoxyethylene (25) oxypropylene monostearate, polyoxyethylene (20) sorbitol monolaurate, polyoxyethylene (23) lauryl ether, polyoxyethylene (50)
30 monostearate, and PEG 4000 monostearate. Alternatively the emulsifier can be

silicone surfactant, especially a dimethyl polysiloxane with polyoxyethylene and/or polyoxypropylene side chains, typically with a molecular weight of 10,000 to 50,000, especially cyclo-methicone and dimethicone copolyol. They may also be provided in the form of vesicular dispersions of ionic or nonionic amphiphilic lipids prepared according to known processes.

The following Examples further illustrate the present invention.

Example 1

Acid Extraction of Manganese Doped Titania

Samples of manganese doped titania were soaked in 25% hydrochloric acid for various times at room temperature. The titania was settled by centrifugation and the supernatant liquid transferred to a 50ml volumetric flask. The titania was washed once by re-suspension in water with the aid of ultrasonics and again centrifuged. The washings were added to the volumetric flask and the contents made to 50 ml. with de-ionised water.

Samples of the extracts, together with the original powder samples, were analysed for manganese. The water extracts were analysed directly by AAS (Atomic Absorption Spectroscopy). The powders were similarly analysed, after digestion with a hydrofluoric acid-sulphuric acid mixture.

DPPH (Radical Scavenging) Assay.

A stock solution of 1mM DPPH in MeOH was made. Samples containing 120µl of DPPH (1mM) plus 300µl TiO₂ (3 mg/ml) were made up to 3ml with MeOH and were placed in a 10 mm quartz cuvette. DPPH is a stable radical, which absorbs at 520nm, therefore a loss of absorbance at this wavelength, is a measure of the radical scavenging ability of the TiO₂. The titania samples were taken from the above series of extractions. The samples were kept in the dark and the absorbance at 520 nm measured every 5 minutes. The samples required mixing before each measurement was taken in order to redisperse the TiO₂.

5

Time of exposure (hrs)	Extracted Mn (%)	Rate of loss of DPPH (mAbs/min)
0	0	3.4
0.25	3.22	2.05
1.5	4.58	1.6
48	26.0	0.35

It is clear from these data that 74% of the manganese remained after 48 hours. As the rate of loss of DPPH is then very small, it is clear that it is the remaining 26% of the manganese which is in or on the surface which acts to scavenge free radicals. Thus particles having manganese available at the surface will scavenge free radicals.

Example 2

A comparison was made between formulations differing solely in the nature of the TiO₂ incorporated.

Preparation of sunscreen formulations

The sunscreen formulations were based on a procedure by Stanley Black (www.sblack.com Formula Reference 1629).

20 Phase A

	% w/w
Water	80.35
Propylene Glycol	2.00
Methylparaben	0.15
25 Aloe Vera Gel x1	0.10

Phase B

Lexemul 561 (Glyceryl Stearate, PEG-100 Stearate)	5.00
Lexemul GDL (Glyceryl Dilaurate)	1.50
Stearyl Alcohol NF	0.30

	Lexol IPM (Isopropyl Myristate)	1.00
	Lexol EHP (Octyl Palmitate)	2.00
	Dow Corning 200 Fluid 200cs (Dimethicone)	0.50
	Propylparaben	0.10
5	Parsol 1789 (BMDM)	2.00
	Titanium Dioxide	5.00

The formulations were produced as follows:

Heat phase A to 75°C.

10 Heat phase B to 75°C.

Add phase A to phase B with vigorous stirring.

Cool to room temperature with stirring.

The TiO₂ used was as follows:

15 A. TiO₂ doped with manganese to a level of approximately 1 mole %; primary particle size 20-30 nm; crystal form 99% rutile; no coating.

B. Uvinul TiO₂ from BASF

Primary particle size - c.21nm

Crystal form - 75% Anatase/25% Rutile

20 Coating - Trimethylcaprylsilane at 5%

MT100AQ from Tayca Corp

Primary particle size - 15nm

Crystal form - c.100% Rutile

25 Coating - Alumina/silica/alginate acid at up to 30%

The formulations were tested using the DPPH assay technique of Example 1, on artificial skin and using a cuvette and absorbance measurements taken.

Artificial Skin.

Vitro Skin was obtained from IMS Testing Group. The Vitro-Skin was cut into 6.2 x 9 cm rectangles and placed in a closed, controlled-humidity chamber containing 15% glycerin overnight. Sunscreen samples (formulations) were placed on the re-hydrated films at a loading of 2 mg/ml and spread evenly using a latex covered finger. The film was mounted into a 6 x 6 cm glassless slide mount and left to dry for 15 minutes. UV absorbance was measured and then the sample illuminated by a xenon arc solar simulator for 2 hours. Absorbance measurements were recorded following 5, 15, 30, 60, 90 and 120 minutes illumination.

Cuvette

Samples were loaded into a 10 μ m cuvette (approx. sample volume of 4 μ l i.e. liquid). UV absorbance was measured pre-illumination and also following 5, 15, 30, 60, 90 and 120 minutes illumination by a xenon arc solar simulator or a SOL2 solar simulator (Honle UV technology). A comparison with Nivea SPF10 was also made.

For DPPH assay, the formulations contained 2% Parsol 1789 (avobenzene). The results obtained are shown in Figure1. Clearly the scavenging activity of the doped TiO₂ is significantly superior to that of the commercial products, the rate of loss of DPPH being around 3 time greater.

Figure 2 gives the results of light transmission at 360nm at time 0 and at time 120 minutes for formulations containing 2% avobenzene on hydrated artificial skin.

Figure 3 gives the results of light transmission at 360nm for formulations containing 2% avobenzene (AVO) and 5% octylmethoxycinnamate (OMC) on hydrated artificial skin.

Figure 4 gives the results of light transmission at 360nm at time 0 and at time 120 minutes for formulations containing 2% avobenzene in the cuvette

These results clearly show the superiority of the doped TiO₂ in reducing UVA transmission. The fact that the ratios of the values at time 0 and time 120 minutes are significantly different implies that a reduction in free radical load, from both reduced generation and scavenging, is present in the formulations where doped titania is used.

CLAIMS

1. A UV sunscreen composition suitable for cosmetic or topical pharmaceutical use which comprises: (a) one or more organic components which are photosensitive and/or which are susceptible to degradation by another ingredient of the composition and/or by undoped TiO_2 and/or by undoped ZnO ; and (b) TiO_2 and/or ZnO which has been surface doped with one or more other elements.
2. A composition according to claim 1 wherein the TiO_2 and/or ZnO is only surface doped.
3. A composition according to claim 1 wherein the TiO_2 and/or ZnO is also bulk doped.
4. A composition according to claim 3 wherein the bulk dopant is different from the or each surface dopant.
5. A composition according to any one of claims 1 to 4 which is an aqueous formulation and the TiO_2 and/or ZnO is only surface doped.
6. A composition according to any one of claims 1 to 4 which is an oily formulation.
7. A composition according to any one of claims 1 to 4 which is an oil-in-water or water-in-oil formulation.
8. A composition according to claim 7 wherein the TiO_2 and/or ZnO is present in both phases.
9. A composition according to any one of the preceding claims wherein the TiO_2 and/or ZnO is coated with a discontinuous layer of hydrophilic or hydrophobic material.
10. A composition according to claim 9 wherein the TiO_2 and/or ZnO is coated with a hydrophobic polymer.
11. A composition according to claim 9 wherein the TiO_2 and/or ZnO is coated first with an oxide of aluminum, zirconium or silicon and then with a long chain carboxylic acid salt.
12. A composition according to any one of the preceding claims wherein the dopant is manganese, cerium, vanadium, selenium, chromium or iron.

13. A composition according to claim 12 wherein the dopant is Mn^{2+} .
14. A composition according to one of the preceding claims wherein the dopant is present in an amount from 0.5 to 2 mole % by weight.
15. A composition according to any one of the preceding claims which includes doped titanium dioxide.
16. A composition according to any one of the preceding claims wherein the titanium dioxide is in rutile form.
17. A composition according to any one of claims 1, 2 and 4 to 11 which includes reduced zinc oxide.
18. A composition according to any one of the preceding claims which has 0.5 to 20 mole % by weight of the doped TiO_2 or ZnO .
19. A composition according to any one of the preceding claims wherein the doped or reduced oxide has a particle size from 1 to 200 nm.
20. A composition according to any one of claims 1 to 18 wherein the doped or reduced oxide has a particle size from 100 to 500 nm.
21. A composition according to any one of the preceding claims wherein one or more of the said organic components is a UV sunscreen agent.
22. A composition according to claim 21 wherein the organic sunscreen agent absorbs UV light in the UVA region.
23. A composition according to claim 21 or 22 wherein the organic sunscreen agent is a paraaminobenzoic acid, ester or derivative thereof, a methoxy cinnamate ester, a benzophenone, a dibenzoylmethane, an alkyl- β,β -phenyl acrylate, a triazine, a camphor derivative, an organic pigment, a silicone based sunscreen agent or 2-phenylbenzimidazolyl-5 sulphonic acid or phenyldibenzimidazolyl sulphonic acid.
24. A composition according to any one of the preceding claims which contains one or more of a fatty substance, organic solvent, silicone, thickener, demulsant, UVB sunscreen agent, antifoaming agent, moisturising agent, perfume preservative, surface activation filler, sequestrant, anionic, cationic, nonionic or amphoteric polymer, propellant, alkalising or acidifying agent, colourant or metal

oxide pigment.

25. A composition according to any one of the preceding claims which is a sunscreen.

5 26. A composition according to claim 1 substantially as hereinbefore described.

27. Use of a doped TiO_2/ZnO as defined in any one of claims 1 to 5 and 9 to 14 to reduce the concentration of one or more organic UV sunscreen agents or other ingredient which is photosensitive and/or is degraded by another ingredient in a UV sunscreen composition.

10 28. A method of increasing the effectiveness of an organic UV sunscreen composition which comprises one or more components which are photosensitive and/or are susceptible to degradation by another ingredient of the composition and/or by undoped TiO_2 and/or by undoped ZnO , which method comprises incorporating into the composition a doped TiO_2/ZnO as defined in any one of claims 1 to 5 and 9
15 to 14.

29. A method of reducing the production of a toxic compound in a UV sunscreen composition which comprises incorporating therein doped TiO_2 and/or ZnO as defined in any one of claims 1 to 5 and 9 to 14.

ABSTRACT

A UV sunscreen composition suitable for cosmetic or topical pharmaceutical use which comprises a UV sunscreen composition suitable for cosmetic or topical
5 pharmaceutical use which comprises one or more organic components which are photosensitive and/or which are degraded by another ingredient of the composition, and TiO_2 and/or ZnO which has been surface doped with another element.

Figure 1

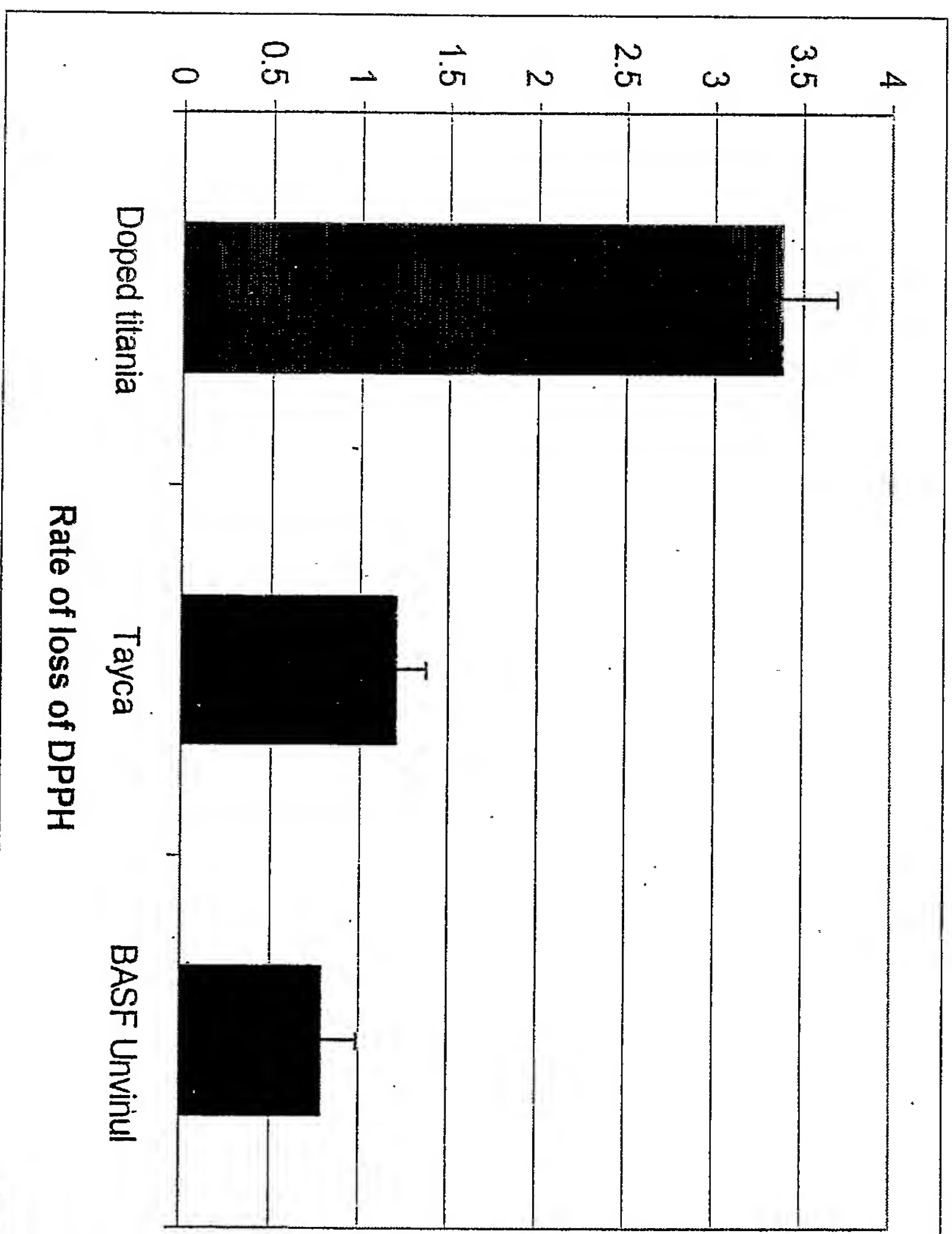




Figure 2

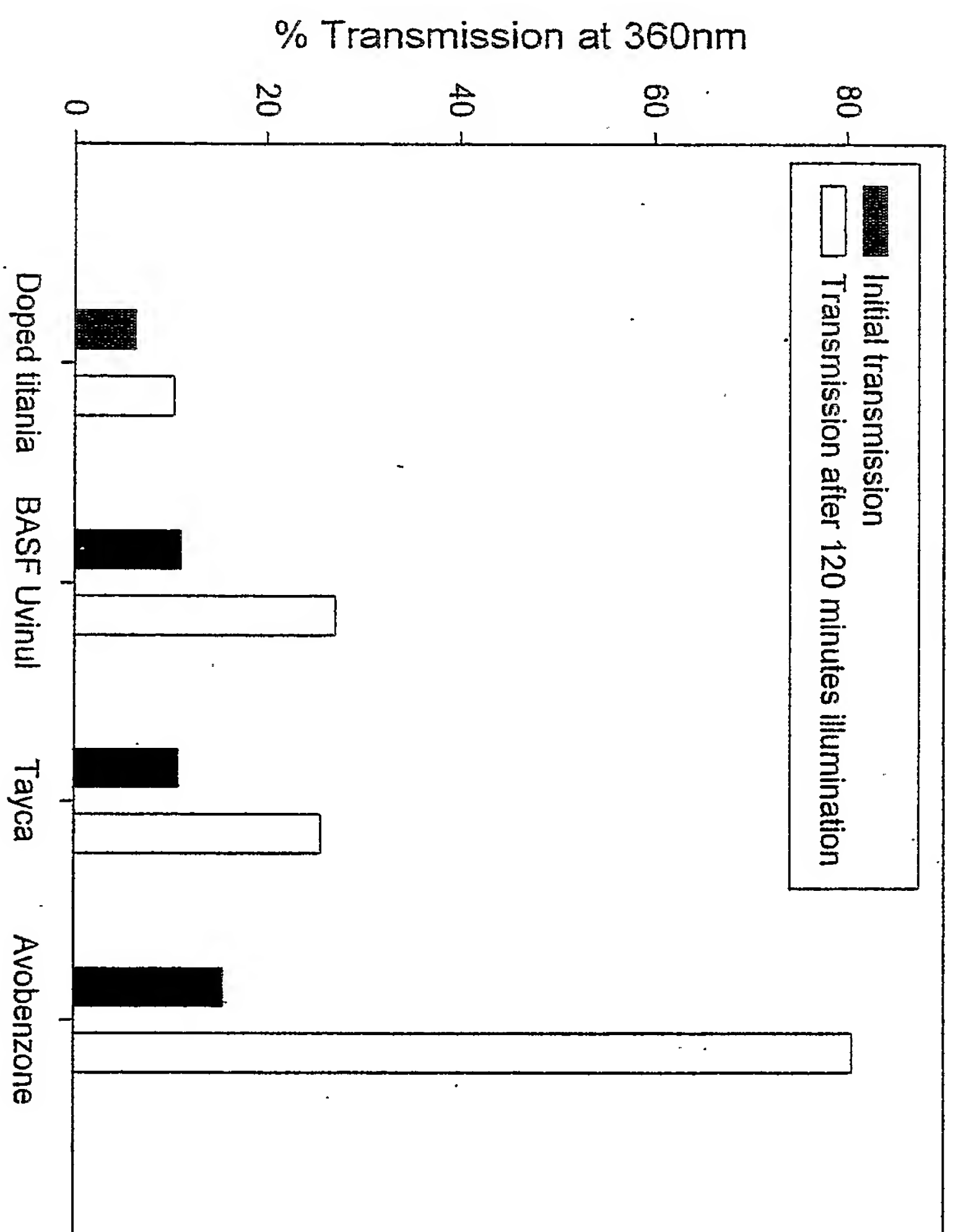




FIGURE 3

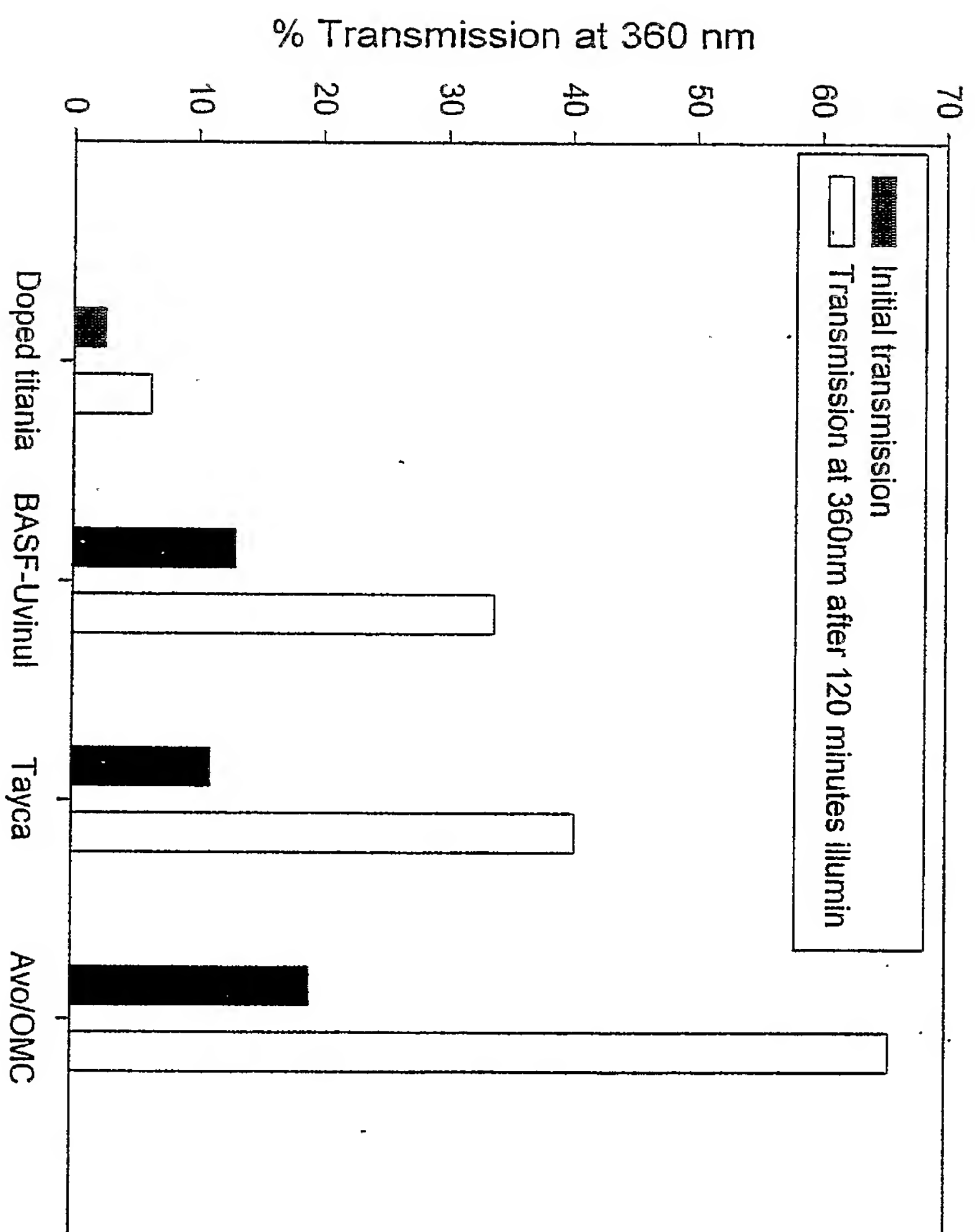




Figure 4

